Clinical Policy: Voxelotor (Oxbryta)

Reference Number: CP.PHAR.451
Effective Date: 03.01.20
Last Review Date: 02.24
Line of Business: Commercial, HIM, Medicaid Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Voxelotor (Oxbryta™) is a hemoglobin S (HbS) polymerization inhibitor.

FDA Approved Indication(s)*

Oxbryta is indicated for the treatment of sickle cell disease (SCD) in adults and pediatric patients 4 years of age and older.

This indication is approved under accelerated approval based on the increase in hemoglobin (Hb). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

***Pfizer, the manufacturer of Oxbryta, announced the voluntary withdrawal of Oxbryta for the treatment of SCD based on the totality of clinical data that indicates the overall benefit of Oxbryta no longer outweighs the risk in this population** (*see Appendix E*)**.**

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Oxbryta is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Sickle Cell Disease

1. Authorization is not permitted. Member may not initiate therapy with Oxbryta. If member is currently using Oxbryta, proceed to section II.A. Sickle Cell Disease for continued therapy (*see Appendix E*).

Approval duration: Not applicable

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Sickle Cell Disease (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy as evidenced by an increase in Hb level from baseline of at least 1 g/dL;
3. Provider attestation acknowledging market withdrawal of Oxbryta and that provider is actively collaborating with the member to establish next steps in the treatment plan;
4. Oxbryta is prescribed concurrently with hydroxyurea, unless contraindicated or clinically significant adverse effects are experienced;
5. Oxbryta is not prescribed concurrently with Adakveo;
6. If request is for a dose increase, new dose does not exceed one of the following (a, b, or c):
   a. Member is concurrently taking a strong CYPA3A4 inducer (*see Appendix D*): 2,500 mg (5 tablets) per day;
   b. Member is concurrently taking a moderate CYPA3A4 inducer (*see Appendix D*): 2,000 mg (4 tablets) per day;
   c. For all other members: 1,500 mg (3 tablets) per day.

Approval duration: 1 month

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
Hb: hemoglobin
SCD: sickle cell disease
VOC: vaso-occlusive crisis

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
hydroxyurea (Droxia®)	*Age ≥ 18 years* Initial: 15 mg/kg/day PO single dose; based on blood counts, may increase by 5 mg/kg/day every 12 weeks to a max 35 mg/kg/day	35 mg/kg/day
hydroxyurea (Siklos®)	*Age ≥ 2 years* Initial: 20 mg/kg/day PO QD; based on blood counts, may increase by 5 mg/kg/day every 8 weeks or if a painful crisis occurs	35 mg/kg/day
L-glutamine (Endari®)	Weight > 65 kg: 15 g (3 packets) PO BID Weight 30 to 65 kg: 10 g (2 packets) PO BID Weight < 30 kg: 5 g (1 packet) PO BID	30 g/day (maximum dose based on weight)

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): prior drug hypersensitivity to Oxbryta or excipients
- Boxed warning(s): none reported

Appendix D: General Information

- A VOC is defined as a previously documented episode of acute painful crisis or acute chest syndrome (ACS) for which there was no explanation other than VOC that required prescription or healthcare professional-instructed use of analgesics for moderate to severe pain.

- Myelosuppression and hydroxyurea treatment failure: Myelosuppression is dose-dependent and reversible and does not qualify for treatment failure. NIH guidelines recommend a 6 month trial on the maximum tolerated dose prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy. A lack of increase in mean corpuscular volume (MCV) and/or fetal hemoglobin (HbF) levels is not indication to discontinue therapy.
- Hydroxyurea dose titration: Members should obtain complete blood counts (CBC) with white blood cell (WBC) differential and reticulocyte counts at least every 4 weeks for titration. The following lab values indicate that it is safe to increase dose.
  - Absolute neutrophil count (ANC) in adults ≥ 2,000/uL, or ANC ≥ 1,250/uL in younger patients with lower baseline counts
  - Platelet counts ≥ 80,000/uL

  If neutropenia or thrombocytopenia occurs: hydroxyurea dosing is held, CBC and WBC differential are monitored weekly, members can restart hydroxyurea when values have recovered.
- Examples of moderate CYP3A4 inducers: bosentan, dabrafenib, efavirenz, mitapivat, modafinil, rifabutin, rifapentine
- Examples of strong CYP3A4 inducers: apalutamide, carbamazepine, phenobarbital, phenytoin, rifampin
- Rationale for the failure of L-glutamine and blood transfusions prior to Oxbryta use: Oxbryta's lack of achieving clinically meaningful endpoints is the rationale for the redirection to agents that do demonstrate clinically meaningful endpoints. While Oxbryta has demonstrated a statistically significant increase of 1.1 g/dL Hb and reduction in hemolysis markers, it's not clear that improved levels of hemoglobin lead to any clinically significant endpoints. There is uncertainty of whether there is a threshold of reduced hemolysis required to achieve clinical benefit. Additionally, the pivotal trial demonstrated that although hemoglobin levels increased with treatment, the rate of pain crises did not decrease. Currently there is no compelling data to support that an increase of 1.1 g/dL hemoglobin level results in a reduction in VOCs or other clinically meaningful outcomes related to SCD.
  - L-glutamine has demonstrated statistically significant reduced acute pain episodes, delay in time to first crisis was delayed, and reduced hospitalizations.
  - Blood transfusions lower the percentage of sickle Hb and increase Hgb oxygen saturation, both of which decrease the propensity for vaso-occlusion and decrease the incidence of SCD-related complications.
- STAND trial results for Adakveo: In a press release Novartis announced that the STAND study did not demonstrate a statistically significant difference between Adakveo 5mg/kg or Adakveo 7.5mg/kg and placebo in annualized rates of VOCs leading to a healthcare visit over the first-year post randomization. These findings are inconsistent with previous trial results from SUSTAIN, which demonstrated the superiority of crizanlizumab 5.0mg/kg compared to placebo.

Appendix E: Oxbryta Market Withdrawal

- Pfizer announced on September 25, 2024 that it was voluntarily withdrawing Oxbryta for the treatment of SCD, as well as discontinuing all active Oxbryta clinical trials and expanded access programs worldwide. Pfizer's decision is based on the totality of clinical

data that indicates the overall benefit of Oxbryta no longer outweighs the risk in the approved sickle cell patient population. The data suggest an imbalance in VOC and fatal events which require further assessment. Oxbryta was originally granted accelerated approval for Oxbryta for treatment of SCD based on the increase in hemoglobin in December 2019.

- Pfizer advised that patients should no longer be prescribed Oxbryta and should contact their physicians to discuss alternative treatment. Additionally, complications when treatment is interrupted abruptly cannot be excluded, but neither efficacy nor a dose for gradual discontinuation have been established.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
SCD	*Age ≥ 12 years* 1,500 mg PO QD with or without food. Strong CYP3A4 inducer: 2500 mg PO QD Moderate CYP3A4 inducer: 2000 mg PO QD *Age 4 to < 12 years* Weight ≥ 40 kg: 1500 mg PO QD • Strong CYP3A4 inducer: 2500 mg PO QD • Moderate CYP3A4 inducer: 2000 mg PO QD Weight 20 kg to < 40 kg: 900 mg PO QD • Strong CYP3A4 inducer: 1500 mg PO QD • Moderate CYP3A4 inducer: 1200 mg PO QD Weight 10 kg to < 20 kg: 600 mg PO QD • Strong or moderate CYP3A4 inducer: 900 mg PO QD	See regimen

VI. Product Availability

- Tablets: 300 mg, 500 mg
- Tablet for oral suspension: 300 mg

VII. References

1. Oxbryta Prescribing Information. South San Francisco, CA: Global Blood Therapeutics, Inc.; August 2023. Available at: https://www.oxbryta.com/. Accessed October 2, 2023.
2. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA*. 2014 Sep 10;312(10):1033-48.
3. Vichinsky E, Hoppe CC, Ataga KI, et al. A phase 3 randomized trial of voxelotor in sickle cell disease. *N Engl J Med*. 2019 Aug 8;381(6):509-519.
4. Micromedex® Healthcare Series [Internet database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically. Accessed October 31, 2022.

5. Brandow A, Carroll C, Creary S, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. *Blood Advances*. 2020;4(12):2656-2701.
6. Migotsky M, Beestrum M, Badawy SM. Recent advances in sickle-cell disease therapies: A review of voxelotor, crizanlizumab, and L-glutamine. Pharmacy (Basel). 2022;10(5):123.
7. Dick MH, Abdelgadir A, Kulkarni VV, et al. Comparing the safety and efficacy of L-glutamine, voxelotor, and crizanlizumab for reducing the frequency of vaso-occlusive crisis in sickle cell disease: A systematic review. Cureus. 2022;14(5):e24920.
8. Novartis. European Commission (EC) adopts decision endorsing CHMP recommendation to revoke the conditional marketing authorization for Adakveo® (crizanlizumab) [Press release]. Available at: https://www.novartis.com/news/european-commission-ec-adopts-decision-endorsing-chmp-recommendation-revoke-conditional-marketing-authorization-adakveo-crizanlizumab. Published August 4, 2024. Accessed August 15, 2023.
9. Pfizer. Pfizer voluntarily withdraws all lots of sickle cell disease treatment Oxbryta® (voxelotor) from worldwide markets [Press release]. Available at: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-voluntarily-withdraws-all-lots-sickle-cell-disease. Published September 25, 2024. Accessed September 25, 2024.

ICD-10-CM Diagnosis Codes that Support Coverage Criteria
The following is a list of diagnosis codes that support coverage for the applicable covered procedure code(s).

ICD-10-CM Code	Description
D57.0*	Hb-SS disease with crisis
D57.1	Sickle-cell disease without crisis
D57.2*	Sickle-cell/Hb-C disease
D57.4*	Sickle-cell thalassemia

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	12.10.19	02.20
Added redirections to blood transfusions and a 6 month trial of Adakveo; finalized HIM line of business; reduced initial approval duration to 2 months from 6 months, and continued therapy approval duration to 6 months from 12 months.	03.04.20	05.20
Added requirement for L-glutamine trial per April SDC and prior clinical guidance.	04.22.20	
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	10.26.20	02.21
1Q 2022 annual review: references reviewed and updated; RT4: updated to reflect pediatric age extension (4-11 years), new dose formulation of tablet for oral suspension, and added criterion for documentation of inability to swallow tablet.	01.10.22	02.22
Template changes applied to other diagnoses/indications.	09.28.22	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2023 annual review: updated maximum dosing requirements to allow dose adjustments for CYPA3A4 inducers; references reviewed and updated.	10.31.22	02.23
Removed Adakveo redirection due to STAND trial results announced by Novartis with rationale added to Appendix D; rationale for sickle cell disease therapy redirections added to Appendix D with references.	08.25.23	11.23
1Q 2024 annual review: no significant changes; references reviewed and updated.	10.31.23	02.24
RT4: removed initial approval criteria due to manufacturer withdrawal; revised continued therapy approval duration to 1 month; added continued therapy criterion for attestation of market withdrawal awareness and collaboration on next steps in the treatment plan; added information regarding the market withdrawal to Appendix E.	10.08.24	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan

retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.